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# The Reaction of Cyclic Nitroenamines with Isocyanates. Synthesis of 1,6-Polymethylene-6-nitromethyl-1,3,5-triazine-2,4-dione Derivatives

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**Summary.** The reactions of cyclic nitroenamines with isocyanates were investigated. It was found that two different products could be obtained: in inert media $\beta$-carbamoyl products were observed and when a strong base was used 1,6-polymethylene-6-nitromethyl-1,3,5-triazine-2,4-dione derivatives were isolated.

**Keywords.** Heterocycles; Anions; Cycloadditions; Cyclizations.

## Introduction

Reactions of nitroenamines with a variety of electrophiles have been well studied [1]. In spite of the presence of the strongly electron-withdrawing nitro group these compounds manifest themselves as 'common' enamines in electrophilic reactions, though the most active electrophiles need to be employed. $\beta$-Substituted products are obtained in all cases. Reactions of the nitroenamines bearing an NH-group with bis-electrophiles are accompanied by the intramolecular attack on the nitrogen atom with the formation of cyclic nitro compounds [2].

Unlike acyclic enamines, only several examples of electrophilic reactions of cyclic enamines **1** are known, with electrophilic attack proceeding at both nucleophilic centers. Thus, the reaction between 2-nitromethyleneazepane (**1b**) and acyl isothiocyanates leads to $\beta$-thiocarbamoyl products, which are easily cyclized to the corresponding pyrimido[1,6-*a*]azepines when briefly heated in acetic acid [3].

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An attempt to acylate nitroenamine **1** ($n = 2$) by means of acetyl chloride affords a mixture of *N*- and *C*-acetylated products [4].

We have previously shown that nitroenamine **1b** in the presence of sodium hydroxide reacted with a variety of electrophiles (acid chlorides, sulfonyl chlorides, isocyanates, isothiocyanates) at the nitrogen atom and the products obtained underwent ring opening giving rise to linear compounds – 7-amino-1-nitro-2-heptanone derivatives [5]. In continuation of this research, in the present work we tried to obtain *N*- and $\beta$-carbamoyl derivatives of cyclic nitroenamines **1a** and **1b**, by carrying out reactions under different conditions – in inert media and in the presence of a strong base.

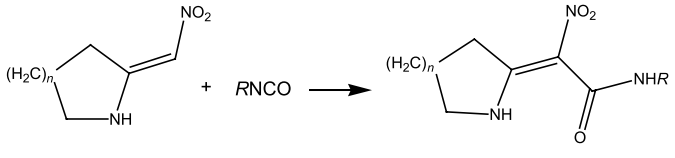
## Results and Discussions

We have found that heating of equimolar amounts of **1a** and **1b** with aryl isocyanates **2a** and **2b** in refluxing toluene lead to $\beta$-carbamoyl nitroenamines **3a–3d**. These results are similar to that of acyclic enamines [6]. Derivatives **3a–3d** are colorless, high-melting compounds, hardly soluble in most organic solvents. Their structure was proved by IR spectra as well as $^1$H and $^{13}$C NMR. IR spectra of **3a–3d** revealed two intensive bands at $\bar{\nu} = 1349$ and $1545\,\mathrm{cm}^{-1}$ corresponding to $\bar{\nu}_{s(NO_2)}$ and $\bar{\nu}_{as(NO_2)}$, and also a band at $1640\,\mathrm{cm}^{-1}$ ($\bar{\nu}_{C=O}$). The absence of a vinyl proton signal at $\delta = 6.3$ ppm in the $^1$H NMR spectra of **3a–3d** which is typical for the starting nitroenamines is an additional evidence for the $\beta$-carbamoyl structure.

It should be noted that the yields of **3a–3d** are dependent on the ring size of **1a** and **1b**. Thus, in case of **1a** ($n = 1$) yields of $\beta$-carbamoyl products are 50–55%, but with $n = 3$ they decrease to 35–40%. Moreover, when a methyl group is attached to the nitrogen atom of **1**, the reaction with aryl isocyanates does not take place at all even after prolonged heating.

We tried to alter the course of the reaction between **1** and isocyanates by using a strong base – sodium hydride. One can assume that under these reaction conditions deprotonation occurs and an electrophilic attack would take place on the nitrogen atom. It was found that treatment of **1a** and **1b** with NaH in dry *DMF* followed by addition of **2a** or **2b** independant of molar ratios lead to the formation of 1,6-polymethylene-6-nitromethyl-1,3,5-triazine-2,4-dione derivatives (**6a–6d**). We rationalized this course of the reaction in Scheme 2.

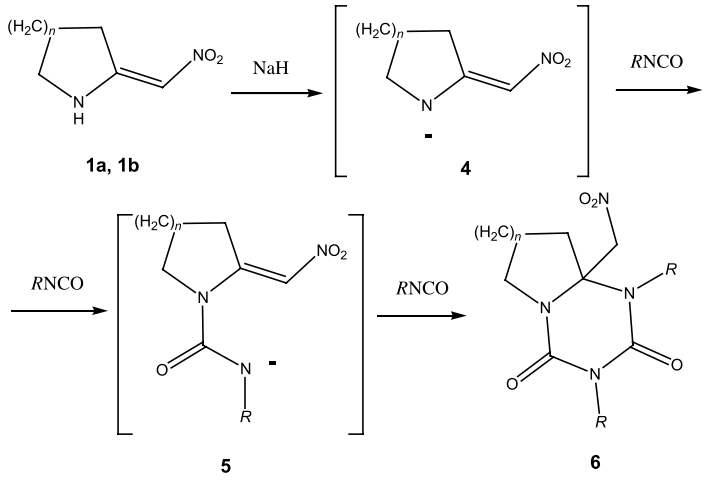
The first step of the reaction is the deprotonation of **1** giving rise to the anion **4**, which undergoes an electrophilic attack at the nitrogen atom. This leads to the formation of **5** with a negative charge on the




**1a, 1b** **2a, 2b** **3a-3d**

**1a, 3a, 3b** $n$ = 1; **1b, 3c, 3d** $n$ = 3; **3a, 3c** $R = C_6H_5$; **3b, 3d** $R$ = 4-$ClC_6H_4$

**Scheme 1**




For compounds **6**: **a, b** $n = 1$; **c, d** $n = 3$; **a, c** $R = Ph$; **b, d** $R = 4\text{-}ClC_6H_4$

**Scheme 2**

nitrogen atom and a highly polarized double bond due to conjugation with the nitro group. Such species may undergo dipolar [4+2]-cycloaddition, which is well-known in isocyanates chemistry. For example, a commonly used method for the synthesis of 1,3,5-triazine-2,4-dione derivatives is an addition of isocyanates to the *Schiff* bases, proceeding *via* formation of a zwitter-ionic intermediate [7]. In a similar way isocyanates react also with amidines. Thus, derivatives of **6** bearing a tertiary amino group instead of the nitromethylene group at the 6-position of the triazine ring are easily accessible from the corresponding cyclic amidines and isocyanates [8]. For the secondary enamines, interaction of this type is not so common, although the reaction of enaminones derived from cyclohexan-1,3-dione with two moles of heterocumulene is known to afford spiro-compounds with a 1,3,5-triazine-2,4-dione moiety [9].

The structures of compounds **6a–6d** are in agreement with their spectra. In IR spectra two bands at $\bar{\nu} = 1385$ and $1550\,cm^{-1}$ ($\bar{\nu}_{NO_2}$) and two intensive bands at 1685 and $1720\,cm^{-1}$ ($\bar{\nu}_{C=O}$) are observed. $^1H$ NMR spectra of **6a–6d** display a signal at 4–5 ppm, which corresponds to the nitromethylene group and appears as AB-system with $J = 11.7$ Hz. As an additional evidence of the bycyclic structure $^{13}C$ NMR spectra of these compounds reveal two signals at 78 and 79 ppm that correspond to the 8a-C/10a-C and nitromethylene group.

Thus, we have found that the reaction of cyclic nitroenamines **1** with isocyanates in inert media afforded $\beta$-carbamoyl products, whereas 1,6-polymethylene-6-nitromethyl-1,3,5-triazine-2,4-dione derivatives were isolated when a strong base was used.

## Experimental

Commercial reagents were used without further purification unless stated. $^1H$ NMR spectra were recorded on a VXR 300 spectrometer in *DMSO*-$d_6$ at 300 MHz. Chemical shifts are expressed in ppm (*TMS*). $^{13}C$ NMR spectra were recorded on a VXR 300 spectrometer in *DMSO*-$d_6$ at 75 MHz. Infrared spectra of KBr discs were obtained on a Perkin-Elmer 1600 FT IR spectrometer. The results of elemental analyses (C, N) were found to be in good agreement ($\pm 0.3\%$) with the calculated values.

*General Method for the Preparation of **3a–3d***

To 4 mmol of **1a** or **1b** in 20 $cm^3$ of dry toluene 4 mmol of **2a** or **2b** were added. The mixture was then heated under reflux for 8 h. The reaction mixture was cooled and held in a refrigerator overnight. The resulting precipitate was filtered off and recrystallized from the solvent indicated.

*2-Nitro-N-phenyl-2-pyrrolidin-2-ylideneacetamide* (**3a**, $C_{12}H_{13}N_3O_3$)

Yield 51%, mp 185–187°C (*DMF-iPr*OH); $^1$H NMR: $\delta = 1.98–2.06$ (m, 4-$CH_2$), 3.10 (t, $J = 7.2$ Hz, 3-$CH_2$), 3.71 (t, $J = 7.2$ Hz, 5-$CH_2$), 6.54 (t, $J = 7.2$ Hz, H-arom), 7.28 (t, $J = 8.1$ Hz, 2H-arom), 7.60 (d, $J = 7.8$ Hz, 2H-arom), 10.56 (bs, NH + NHCO) ppm; $^{13}$C NMR: $\delta = 21.22$ (4-C), 34.82 (3-C), 50.05 (5-C), 117.56, 119.96, 124.07, 129.28, 139.50, 161.31 (CO), 166.02 (2-C) ppm; IR (KBr): $\bar{\nu} = 1640$ (C=O, st), 1545 and 1349 ($NO_2$, st) $cm^{-1}$.

*N-(4-Chlorophenyl)-2-nitro-2-pyrrolidin-2-ylideneacetamide* (**3b**, $C_{12}H_{12}ClN_3O_3$)

Yield 54%, mp 247–249°C (*DMF-iPr*OH); $^1$H NMR: $\delta = 1.98–2.06$ (m, 4-$CH_2$), 3.14 (t, $J = 7.2$ Hz, 3-$CH_2$), 3.73 (t, $J = 7.2$ Hz, 5-$CH_2$), 7.27 (d, $J = 8.7$ Hz, 2H-arom), 7.63 (d, $J = 8.7$ Hz, 2H-arom), 10.60 (bs, NH), 10.67 (bs, NHCO) ppm; $^{13}$C NMR: $\delta = 21.21$ (4-C), 34.75 (3-C), 50.08 (5-C), 117.40, 121.49, 127.59, 129.20, 138.48, 161.42 (CO), 165.89 (2-C) ppm; IR (KBr): $\bar{\nu} = 1640$ (C=O, st), 1545 and 1349 ($NO_2$, st) $cm^{-1}$.

*2-Azepan-2-ylidene-2-nitro-N-phenylacetamide* (**3c**, $C_{14}H_{17}N_3O_3$)

Yield 37%, mp 208–211°C ($CHCl_3$-*iPr*OH); $^1$H NMR: $\delta = 1.60–1.77$ (m, 4-$CH_2$, 5-$CH_2$, 6-$CH_2$), 2.49–2.60 (m, 3-$CH_2$), 3.64–3.69 (m, 7-$CH_2$), 7.04 (t, $J = 7.2$ Hz, 1H-arom), 7.28 (t, $J = 8.1$ Hz, 2H-arom), 7.60 (d, $J = 7.8$ Hz, 2H-arom), 10.41 (bs, NHCO), 10.83 (bs, NH) ppm; $^{13}$C NMR: $\delta = 24.18$, 28.02, 29.64, 30.64 (3-C), 44.77 (7-C), 120.76, 121.17, 124.77, 129.28, 138.64, 161.30 (CO), 164.77 (2-C) ppm; IR (KBr): $\bar{\nu} = 1643$ (C=O, st), 1543 and 1347 ($NO_2$, st) $cm^{-1}$.

*2-Azepan-2-ylidene-N-(4-chlorophenyl)-2-nitroacetamide* (**3d**, $C_{14}H_{16}ClN_3O_3$)

Yield 39%, mp 255–257°C (*DMF-iPr*OH); $^1$H NMR: $\delta = 1.51–1.72$ (m, 4-$CH_2$, 5-$CH_2$, 6-$CH_2$), 2.63–2.70 (m, 3-$CH_2$), 3.64–3.69 (m, 7-$CH_2$), 7.36 (d, $J = 8.7$ Hz, 2H-arom), 7.64 (d, $J = 8.7$ Hz, 2H-arom), 10.61 (bs, NHCO), 10.82 (bs, NH) ppm; $^{13}$C NMR: $\delta = 24.18$, 28.02, 29.64, 30.64 (3-C), 44.77 (7-C), 120.76, 121.17, 127.77, 129.28, 138.64, 161.30 (CO), 164.77 (2-C) ppm; IR (KBr): $\bar{\nu} = 1643$ (C=O, st), 1543 and 1347 ($NO_2$, st) $cm^{-1}$.

*General Method for the Preparation of **6a–6d***

To a solution of 4 mmol of **1a** or **1b** in 20 $cm^3$ of dry *DMF* 4 mmol of *NaH* (60% suspension in mineral oil) were added. The mixture was stirred vigorously for 0.5 h until the evolution of $H_2$ had ceased. Then 8 mmol of **2a** or **2b** were added and stirring was continued for another 5 h. The reaction mixture was diluted with twice of its volume of $H_2O$ and filtered. The filtrate was brought to $pH = 1$ by HCl addition and the resulting precipitate was filtered off and recrystallized from the solvent indicated.

*8a-Nitromethyl-1,3-diphenyltetrahydropyrrolo[1,2-a][1,3,5]triazine-2,4-dione* (**6a**, $C_{19}H_{18}N_4O_4$)

Yield 65%, mp 196–198°C (*Et*OH-$CHCl_3$); $^1$H NMR: $\delta = 1.72–1.84$ (m, 1H), 1.98–2.10 (m, 2H), 2.34–2.47 (m, 1H), 3.62–3.71 (m, 1H), 3.82–3.93 (m, 1H), 4.94 (dd, $J = 11.7$ Hz, $CH_2NO_2$), 7.17 (d,

$J = 6.9$ Hz, 2H-arom), 7.30–7.51 (m, 8H-arom) ppm; $^{13}$C NMR: $\delta = 20.08$ (7-C), 37.86 (8-C), 47.02 (6-C), 78.10 (8a-C), 79.71 (C-$NO_2$), 128.45, 129.03, 129.37, 129.43, 130.02, 130.75, 136.13, 137.38, 149.74 (CO), 151.76 (CO) ppm; IR (KBr): $\bar{\nu} = 1685$ and 1725 (C=O, st), 1550 and 1385 ($NO_2$, st) cm$^{-1}$.

*1,3-Bis(4-chlorophenyl)-8a-nitromethyltetrahydropyrrolo[1,2-a][1,3,5]triazine-2,4-dione* (**6b**, $C_{19}H_{16}Cl_2N_4O_4$)

Yield 73%, mp 208–210°C (*DMF-iPr*OH); $^1$H NMR: $\delta = 1.76$–1.86 (m, 1H), 1.94–2.08 (m, 2H), 2.30–2.44 (m, 1H), 3.58–3.72 (m, 1H), 3.76–3.89 (m, 1H), 4.94 (dd, $J = 11.4$ Hz, $CH_2NO_2$), 7.14 (d, $J = 8.4$ Hz, 2H-arom), 7.40 (d, $J = 8.4$ Hz, 2H-arom), 7.46–7.59 (m, 4H-arom) ppm; $^{13}$C NMR: $\delta = 20.10$ (7-C), 37.67 (8-C), 47.11 (6-C), 78.14 (8a-C), 79.71 (C-$NO_2$), 129.17, 130.10, 131.21, 132.61, 133.14, 134.07, 134.89, 136.11, 149.47 (CO), 151.51 (CO) ppm; IR (KBr): $\bar{\nu} = 1687$ and 1726 (C=O, st), 1549 and 1386 ($NO_2$, st) cm$^{-1}$.

*10a-Nitromethyl-1,3-diphenylhexahydro[1,3,5]triazino[1,2-a]azepine-2,4-dione* (**6c**, $C_{21}H_{22}N_4O_4$)

Yield 47%, mp 254–256°C (*Et*OH-$CHCl_3$); $^1$H NMR: $\delta = 1.26$–1.92 (m, 7-$CH_2$, 8-$CH_2$, 9-$CH_2$, 10-$CH_2$), 3.35 (m, 1H), 4.14 (m, 1H), 4.91 (dd, $J = 11.7$ Hz, $CH_2NO_2$), 7.12 (d, $J = 6.9$ Hz, 2H-arom), 7.31–7.58 (m, 7H-arom), 7.67 (d, $J = 7.2$ Hz, 1H-arom) ppm; $^{13}$C NMR: $\delta = 21.38$, 28.69, 28.99, 35.42 (10-C), 42.62 (6-C), 78.58 (10a-C), 79.27 (C-$NO_2$), 128.35, 128.93, 129.34, 130.01, 130.23, 131.17, 136.33, 137.72, 151.03 (CO), 151.81 (CO) ppm; IR (KBr): $\bar{\nu} = 1685$ and 1725 (C=O, st), 1550 and 1385 ($NO_2$, st) cm$^{-1}$.

*1,3-Bis(4-chlorophenyl)-10a-nitromethylhexahydro[1,3,5]triazino[1,2-a]azepine-2,4-dione* (**6d**, $C_{21}H_{20}Cl_2N_4O_4$)

Yield 51%, mp 246–248°C (*Et*OH-$CHCl_3$); $^1$H NMR: $\delta = 1.22$–1.92 (m, 7-$CH_2$, 8-$CH_2$, 9-$CH_2$, 10-$CH_2$), 3.35 (m, 1H), 4.14 (m, 1H), 5.09 (dd, $J = 11.7$ Hz, $CH_2NO_2$), 7.17 (d, $J = 6.9$ Hz, 2H-arom), 7.35–7.58 (m, 6H-arom) ppm; $^{13}$C NMR: $\delta = 21.38$, 28.69, 28.99, 35.42 (10-C), 42.62 (6-C), 78.58 (10a-C), 79.27 (C-$NO_2$), 128.35, 129.34, 130.01, 130.14, 130.23, 131.17, 136.33, 137.72, 151.03 (CO), 151.81 (CO) ppm; IR (KBr): $\bar{\nu} = 1685$ and 1725 (C=O, st), 1550 and 1385 ($NO_2$, st) cm$^{-1}$.

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